
Clubbing: An update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance

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Finger clubbing can be a striking physical finding. At other times, the presence of clubbing is difficult to establish by subjective examination alone and the profile angle or distal phalangeal to interphalangeal depth ratio are needed to confirm the finding. Most microscopic and imaging studies of clubbed fingers reveal hypervascularization of the distal digits. Recent research shows that when platelet precursors fail to become fragmented into platelets within the pulmonary circulation, they are easily trapped in the peripheral vasculature, releasing platelet-derived growth factor and vascular endothelial growth factor, promoters of vascularity and, ultimately, clubbing. Clinically, clubbing is associated with a number of neoplastic, pulmonary, cardiac, gastrointestinal, infectious, endocrine, psychiatric, and multisystem diseases. In narrowing the differential diagnosis, we recommend a detailed history and physical examination accompanied by focused laboratory and imaging studies. An algorithm for the evaluation of newly diagnosed clubbing is suggested. (*J Am Acad Dermatol* 2005;52:1020-8.)

Although digital clubbing was recognized as long ago as 400 BC, when Hippocrates described the phenomenon in a patient with empyema, the diagnosis, pathophysiology, and clinical relevance of clubbing remain controversial.¹ This article reviews the recent medical literature as it relates to diagnostic techniques, imaging, differential diagnosis, pathophysiology, and prognosis of digital clubbing. Finally, we suggest an algorithm for the evaluation of newly diagnosed clubbing.

Digital clubbing, alternatively called Hippocratic fingers, watch-glass nails, or drumstick fingers,² can be an isolated finding or may occur as part of the syndrome of hypertrophic osteoarthropathy (HOA). HOA is characterized by periostosis of long bones, joint pain, and clubbing³; it may be primary, also known as pachydermoperiostosis, or secondary to a variety of disease processes. A review of the history of HOA in the medical literature has been published previously.⁴

Primary HOA is an autosomal dominant disorder that presents in otherwise healthy children as clubbing, periostosis, and skin manifestations including thickening of the skin of the face and scalp, coarsening of facial features, hyperhidrosis, and seborrhea. Incomplete forms of primary HOA may present

as isolated finger clubbing, periostosis, or pachydermia.⁵ What was once called familial clubbing in the literature was most likely an incomplete form of primary HOA.⁶

Like primary HOA, secondary HOA may also present as the full spectrum of HOA or as isolated finger clubbing. Clubbing in secondary HOA may be unilateral or bilateral. Unilateral clubbing has been associated with neurologic and vascular diseases (Table I). Although many clinicians are familiar with the strong association between secondary HOA (including bilateral clubbing) and pulmonary neoplasms, bilateral clubbing has been associated with other neoplastic, pulmonary, cardiac, gastrointestinal, infectious, endocrine, psychiatric, and multisystem diseases as well (Table II).

Clubbing has been described as occurring in stages.^{4,2} First, there is a periungual erythema and a softening of the nail bed, giving a spongy sensation on palpation, followed by an increase in the normal 160° angle between the nail bed and the proximal nailfold. This increased angle causes the nail to develop a convexity as it grows. Eventually the nail and periungual skin appear shiny and the nail develops longitudinal ridging. The depth of the distal phalange increases and the distal interphalangeal joint may become hyperextensible.^{4,2} Clubbing usually develops over years but in certain conditions may develop subacutely.

DIAGNOSIS

Clinical

Researchers have described many techniques for the accurate diagnosis of clubbing. Recognizing that

From the Department of Dermatology, University of Pittsburgh.
Funding sources: None.

Conflicts of interest: None identified.

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0190-9622/\$30.00

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doi:10.1016/j.jaad.2005.01.006

Table I. Diseases associated with unilateral clubbing

Disease	Study	Findings
Hemiplegia	Alvarez et al 1975 ⁷	Of 87 patients with hemiplegia, 12 had clubbing on affected side
	Siragusa et al 2001 ⁸	Of 108 patients with hemiplegia, two had clubbing on affected side vs none of the control subjects
Vascular lesions	Leb and Sharma 1978 ⁹	One patient with dialysis fistula had clubbing on ipsilateral aspect of hand
	Kaditis et al 1995 ¹⁰	One patient with Takayasu's arteritis of aortic arch and left subclavian artery had clubbing on left hand
	Abe et al 1999 ¹¹	One patient with ulnar artery aneurysm had clubbing on ipsilateral aspect of hand

None of the authors noted that a method of diagnosis other than subjective physical examination was used to diagnose clubbing.

the presence or absence of clubbing was not always obvious at the bedside, Lovibond⁴³ was among the first to offer a criteria for the diagnosis of finger clubbing. Lovibond⁴³ defined the "profile sign" of the thumb, or Lovibond's angle as it came to be known, as the angle made by the nail as it exits the proximal nailfold. He reported that a profile sign of greater than 180 degrees could be used to differentiate true clubbing from other conditions such as simple nail curving and paronychia, which retained an angle closer to 160 degrees. Curth et al⁴⁴ found that the fingers of members of a family affected by familial clubbing were notable for a marked decrease in the angle between the back surface of the middle phalanx and that of the terminal phalanx, from 160 degrees in control subjects to 145 degrees in affected patients; they called this angle the "modified profile angle." The authors note, however, that they prefer the use of Lovibond's original profile angle to detect more subtle clubbing.⁴⁴ Rice and Rowland⁴⁵ were the first to measure the ratio of distal phalangeal to interphalangeal depth of the middle finger; they determined that a value greater than 1.1 could be used to define clubbing. Regan et al⁴⁶ reported that a diagnosis of clubbing based on a hyponychial angle of 209.4 degrees was correlated with physicians' subjective determination of clubbing in the digital casts of 50 asbestos workers. They defined the hyponychial angle as the angle made by the intersection of a line drawn from the "distal digital crease" (or back surface of the distal interphalangeal joint) to the cuticle with a line drawn from the cuticle to the hyponychium. Amidst his personal experience with infective endocarditis, Schamroth⁴⁷ observed that the normal diamond-shaped window created by placing the back surfaces of opposite terminal phalanges together was obliterated in clubbing. More recently, Myers and Farquhar⁴⁸ extensively reviewed the published criteria for the diagnosis of clubbing and recommended that, in cases of diagnostic uncertainty, a profile angle of greater than 180 degrees

and a distal phalangeal to interphalangeal depth ratio of greater than 1.0 may be used to better characterize the presence of clubbing. Finally, recent authors have recommended the use of digital photography to aid in the measurement of nail angles⁴⁹ and in the distinction between clubbing and simple nail curving.⁵⁰ Although it has been our experience that dermatologists and internists are most likely to use the loss of the diamond-shaped window to evaluate for clubbing, we have found that subjective assessment of distal phalangeal to interphalangeal depth ratio is convenient when the diamond-shaped window is not helpful (Figs 1 and 2).

Imaging

There are many reports of the radiographic findings of HOA, but there are no reports of plain radiographs of isolated clubbed nails in the absence of HOA. There are numerous reports of angiography of clubbed nails. Most reports of arteriography of the hands of patients with clubbing show hypervascularization, manifested as an increase in the number and size of distal digital arteries or arteriovenous communications,^{51,52} but one group found no difference in postmortem angiograms between patients with and without clubbing.⁵³ A single report of magnetic resonance angiography of a clubbed hand showed hypervascularization.⁵⁴ Positron emission tomography scans comparing two patients with lung cancer, one with and one without clubbing, revealed increased glucose metabolism in all of the digits of the fingertips of the patient with clubbing.⁵⁵

Pathology

Most reports of the microscopic pathology of clubbing investigate the affected skin of patients with primary HOA. One case report of a patient with primary HOA with clubbing included sampling of the periungual border and fingertip skin during surgical reduction of the distal phalanges as treatment of hand pain.⁵⁶ Light microscopy of fingertip

Table II. Diseases associated with bilateral clubbing

Disease	Study	Findings
Neoplastic		
Bronchogenic carcinoma	Sridhar et al 1998 ¹²	Of 111 patients with lung cancer, 32 had clubbing; 35% of NCSLC vs 4% of SCLC (loss of 15-degree angle between nail and cuticle)
Pleural tumors	Rena et al 2001 ¹³	Of 21 patients, 14.3% had clubbing
Lymphoma	Nasr et al 1976 ¹⁴ Kebudi et al 1997 ¹⁵	Of 40 patients with Mediterranean lymphoma, 6 had clubbing Review of 5 cases of intrathoracic Hodgkin's in children, all with clubbing and HOA
Nasopharyngeal carcinoma	Leung et al 1991 ¹⁶	Of 90 patients with metastatic disease, 6 had clubbing
Mesothelioma	McGavin and Hughes 1998 ¹⁷	Of 77 patients, 23 had fluctuation of the nail bed vs 14% of patients with benign asbestos pleural disease
Pulmonary		
CF	Pitts-Tucker et al 1986 ¹⁸	73 Patients with CF had a mean hyponychial angle of 192 degrees
Asbestosis	Coutts et al 1987 ¹⁹	Of 167 patients, 72 had clubbing at time of asbestosis diagnosis
Hypersensitivity pneumonitis	Sansores et al 1990 ²⁰	Of 82 patients, 44 had clubbing at time of diagnosis (retrospective chart review)
IPF	Johnston et al 1997 ²¹	Of 588 patients, 289 had clubbing at time of IPF diagnosis
Pulmonary AVM	Swanson et al 1999 ²²	Of 93 patients with pulmonary AVM, 18 had clubbing (retrospective chart review)
HPS	Martinez et al 2001 ²³	Of 14 patients with cirrhosis, 9 patients with HPS had clubbing vs 5 of 66 patients with cirrhosis without HPS
Sarcoidosis	Gupta et al 1985 ²⁴	Of 90 Indian patients, 11 had clubbing
Cardiac		
Cyanotic heart disease	McLaughlin et al 1967 ²⁵	Case report of two children with cyanotic heart disease presenting with clubbing and HOA
Gastrointestinal		
IBD	Kitis et al 1979 ²⁶	75 of 200 Patients with Crohn's disease and 15 of 103 patients with ulcerative colitis had clubbing (hyponychial angle)
Liver disease	Epstein et al 1981 ²⁷	24% Of patients with primary biliary cirrhosis, 29% of patients with chronic active hepatitis, and 24% of patients with mixed liver disease had clubbing (profile angle)
Celiac sprue	Mohindra et al 2001 ²⁸	Of 42 Indian children with celiac disease, 6 had clubbing
Juvenile polyposis coli	Grosfeld and West 1986 ²⁹	Of 5 children with aggressive polyposis, two also had clubbing
Infectious		
TB	Kaplan and Munson 1941 ³⁰	Of 426 patients with TB, 72 had clubbing
Infective endocarditis	Lowes et al 1980 ³¹	Clubbing was "nearly as common" as heart failure which was found in "nearly half of the [60] patients" with infective endocarditis
Chronic parasite infection	Bowie et al 1978 ³²	All 10 African children infected with <i>Trichuris trichiura</i> (whipworm) had marked clubbing
	Ayad El-Masry et al 1986 ³³	Of 108 Egyptian farmers with schistosomal colonic polyposis, 61 had clubbing
HIV	Rubinstein et al 1986 ³⁴	All 11 children with pulmonary lymphoid hyperplasia secondary to AIDS had clubbing
	Cribier et al 1998 ³⁵	Of 155 HIV-positive patients, 9 had clubbing vs none of the HIV-negative control subjects
Endocrine		
Thyroid disease	Fatourechhi et al 2002 ³⁶	Of 178 patients with thyroid dermopathy, 35 had clubbing
Vascular		
Venous stasis	Sarteel et al 1985 ³⁷	Unreferenced literature review suggests that clubbing is associated with venous stasis but does not provide clinical evidence
Psychiatric		
Laxative abuse	Pines et al 1983 ³⁸	Case report of two patients who abused laxatives with finger clubbing and a review of 4 previously published cases

Table II. Cont'd

Disease	Study	Findings
Multisystem Lupus erythematosus	Mackie 1973 ³⁹	Case report of a female patient with photosensitivity, malar rash, ANA positivity, hyperkeratotic lesions on palms, and finger clubbing
CINCA syndrome	Prieur et al 1987 ⁴⁰	In 30 patients with CINCA (a chronic inflammatory disease that presents in infancy) clubbing was a "common" morphologic characteristic
POEMS syndrome	Dispenzieri et al 2003 ⁴¹	Of 99 patients with POEMS (a plasma cell dyscrasia that presents in the fifth or sixth decade) 5 had recognized finger clubbing

ANA, Antinuclear antibody; AVM, arteriovenous malformation; CF, cystic fibrosis; CINCA, chronic, infantile, neurologic, cutaneous, and articular; HOA, hypertrophic osteoarthropathy; HPS, hepatopulmonary syndrome; IBD, inflammatory bowel disease; IPF, interstitial pulmonary fibrosis; NCSLC, nonsmall cell lung cancer; SCLC, small cell lung cancer; TB, tuberculosis.

If the authors noted that a method of diagnosis other than subjective physical examination was used to diagnose clubbing, it was noted in parentheses.

skin showed diffuse endothelial hyperplasia with partial occlusion of the capillary lumen, a pericapillary lymphohistiocytic infiltrate, hyalinosis, sclerosis with thickening and packing of collagen fibers, and sebaceous and eccrine hypertrophy.⁵⁷ Electron microscopy of the fingertip skin showed both ectasic and hypertrophic capillaries; activated endothelia; thickened, reduplicated capillary basal membranes; and a perivascular infiltrate.⁵⁷

Capillaroscopy studies show that clubbed digits have more splayed and arborized capillary loops and greater capillary plexus formation.⁵⁷

Despite these positive findings, the largest study of clubbing histology to date demonstrated no difference between the microscopic appearance of sections of clubbed phalangeal tissue compared with normal phalangeal tissue.⁵³ The authors specifically comment that the number and appearance of Sucquet-Hoyer anastomoses, which are arteriovenous anastomoses involved in temperature regulation, were unaltered. Considering this inconsistent finding, the pathology of clubbing remains a controversy. Immunohistochemical studies using vascular and smooth muscle markers may be useful in determining if there is a true increase in vascularity, but to our knowledge, these studies have not been reported.

DIFFERENTIAL DIAGNOSIS

Many diseases have been associated with secondary clubbing with or without HOA. Tables I and II provide an overview.

PATHOPHYSIOLOGY

Numerous hypotheses of the pathophysiology of clubbing have been proposed over the years. One group proposed a neurocirculatory reflex based on a patient with an ulnar artery aneurysm and subse-

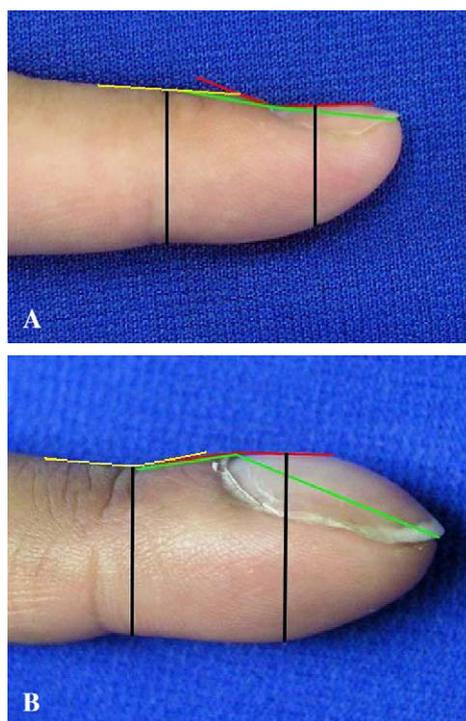


Fig 1. Profile sign/Lovibond sign (red line); modified profile sign (yellow line); hyponychial angle (green line); and distal phalangeal to interphalangeal depth ratio (black line). Normal (A) and clubbed (B) fingers.

quent ipsilateral finger clubbing.⁵⁸ The authors hypothesized that clubbing is associated with local arteriovenous anastomoses provoked by alterations in vascular dynamics that allow blood to bypass capillaries; these anastomoses are actually neurohumoral end organs that allow the autonomic nervous system to regulate the digital microcirculation. Although they suggest that cholinergic fibers and the vagus nerve constitute, respectively, the efferent

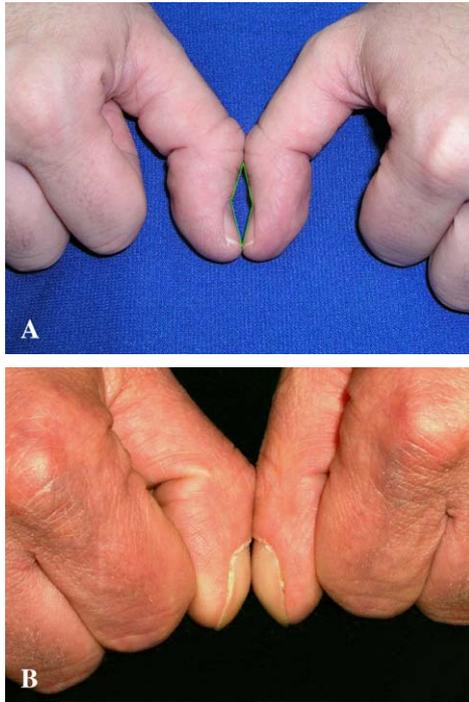


Fig 2. Normal (A) and obliterated (B) Schamroth's sign in clubbing.

and afferent limbs of the reflex, there has been no follow-up to date.

In another study, patients with bronchial carcinoma and clubbing had greater plasma growth hormone levels than patients with bronchial cancer without clubbing and control subjects without clubbing, prompting the authors to identify growth hormone as the cause of clubbing.⁵⁹ However, a subsequent study found no relationship between clubbing and serum growth hormone in a similar sample of patients with lung cancer.⁶⁰

By far the most promising hypothesis has been that of Dickinson and Martin,⁶¹ who based their proposal on emerging evidence of the physiology of platelet production, which showed that megakaryocytes are normally fragmented into platelets in the lungs. The authors propose that processes that disrupt the normal pulmonary circulation, such as chronic lung inflammation, bronchial tumors, or intracardiac right-to-left shunts, would, therefore, allow whole megakaryocytes to enter the systemic circulation. When their large size causes them to become impacted in the fingertip circulation, megakaryocytes and megakaryocyte fragments are activated to release platelet-derived growth factor (PDGF). PDGF promotes growth, vascular permeability, and monocyte and neutrophil chemotaxis, and leads to an increased number of vascular smooth muscle cells and fibroblasts, all of which are seen in

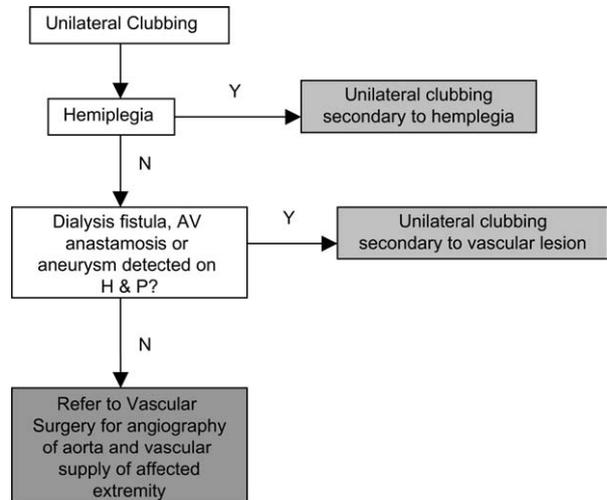


Fig 3. Algorithm for evaluation of unilateral clubbing. AV, Arteriovenous; H&P, history and physical examination; N, no; Y, yes.

the pathology of clubbing. Regarding the myriad disease processes associated with clubbing, Dickinson and Martin⁶¹ point out that inflammatory bowel disease is often associated with a thrombocytopenia and liver disease can be accompanied by pulmonary arteriovenous malformations.

The megakaryocyte/platelet theory of the pathogenesis of clubbing has been supported by several subsequent studies. Patients with cyanotic heart disease and secondary HOA had a lower platelet count and higher mean platelet volume than control subjects, indicating larger platelets and less fragmentation of megakaryocytes in the lungs.⁶² Necropsy of clubbed fingers showed more platelet microthrombi than in control subjects, indicating more platelet activation.⁶³ Patients with primary and secondary HOA had greater PDGF levels than control subjects and patients with lung disease without HOA.⁶⁴

Another platelet-derived, growth-promoting cytokine, vascular endothelial growth factor, is elevated in the serum of patients with lung cancer and secondary HOA compared with patients with lung cancer without HOA, and likely contributes to the vascular hyperplasia seen in clubbing pathology.⁶⁵ Finally, immunohistochemical studies of the stroma of clubbed digits show greater PDGF and vascular endothelial growth factor positivity than that of control subjects; researchers suggest that vascular endothelial growth factor and PDGF are released after platelet impaction and expression is enhanced by hypoxia in the stroma after capillary occlusion.⁶⁶

The megakaryocyte/platelet theory, however, does not explain all of the disease processes associated with clubbing. The unilateral clubbing associated

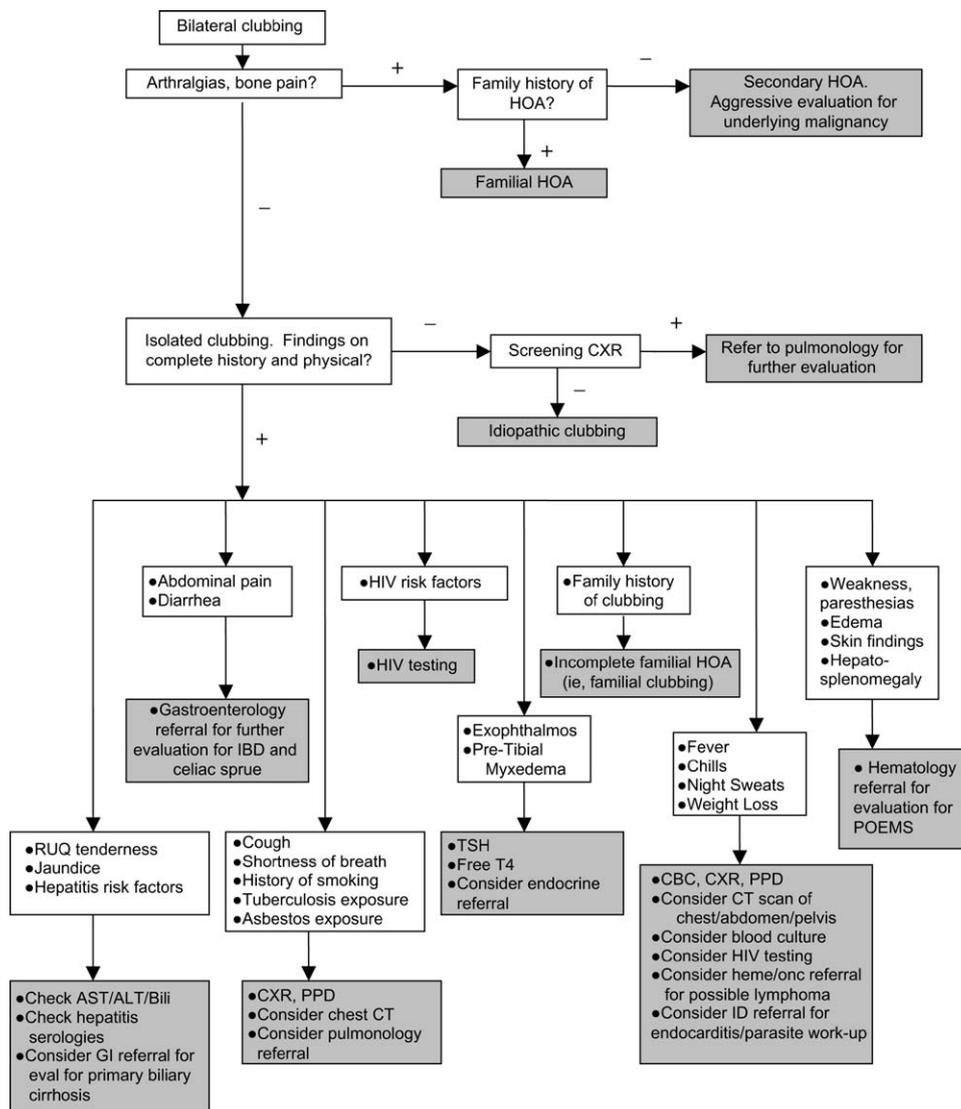


Fig 4. Algorithm for evaluation of bilateral clubbing. *ALT*, Alanine aminotransferase; *AST*, aspartate aminotransferase; *CBC*, complete blood cell count; *CT*, computed tomography; *CXR*, chest radiograph; *GI*, gastrointestinal; *HOA*, hypertrophic osteoarthropathy; *IBD*, inflammatory bowel disease; *ID*, infectious disease; *POEMS*, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; *PPD*, purified protein derivative; *RUQ*, right upper quadrant; *TSH*, thyroid-stimulating hormone.

with hemiplegia⁶⁷ and other local disorders is not easily ascribed to a pulmonary circulation defect. Likewise, it remains to be seen how the pathophysiology of clubbing fits within the pathophysiology of HOA. Dickinson and Martin⁶¹ suggest that an additional factor is necessary to produce the syndrome of HOA whereas other authors hypothesize that cyanosis is necessary, in addition to abnormal platelet function, to produce HOA.⁶⁵

EVALUATION

In evaluating a patient with new-onset clubbing, it is first important to verify that the patient has true

clubbing and not pseudoclubbing. Pseudoclubbing usually involves only a single digit. The digit may appear at first glance to be truly clubbed but, on closer inspection, the profile angle will likely be normal. Pseudoclubbing of a single digit can be seen in patients with a subungual tumor,⁶⁸ pseudocyst,⁶⁹ or osteoid osteoma.⁷⁰ Generalized pseudoclubbing can be seen in disease processes that cause acro-osteolysis,⁷¹ and a number of genetic disorders that cause dysmorphic terminal phalanges.⁷²

Once the diagnosis of clubbing is confirmed by clinical examination, evaluation centers on

differentiating primary clubbing (or primary HOA) from secondary clubbing (or secondary HOA). Unfortunately, appearance of the digits and radiologic examination of the digits do not help in making this distinction. A comprehensive history and physical examination with directed laboratory studies based on the findings is the most appropriate approach.

For patients with unilateral clubbing, the patient will likely provide a history of either a neurologic insult resulting in hemiplegia or a local trauma resulting in aneurysm. If the history and physical do not reveal a dialysis fistula or obvious arterial aneurysm, the dermatologist may outline the risks and benefits of arterial imaging and refer the patient to vascular operation for evaluation of the thoracic aorta and brachial circulation by angiography. The patient and clinician may choose to start with a less invasive but also less sensitive test such as the erythrocyte sedimentation rate; however, a recent prospective study⁷³ of 2683 outpatient angiograms revealed no deaths attributable to angiography and a complication rate of 22%, including hematoma, local pain, rash, nausea, abdominal pain, and leg pain (Fig 3).

For patients with bilateral clubbing, a complete history and physical examination will allow the clinician to narrow the differential diagnosis. A review of systems should focus on constitutional, pulmonary, gastrointestinal, and musculoskeletal symptoms for evidence of malignancy, infection, or inflammation. It is especially important to consider whether clubbing exists with other symptoms of HOA, particularly bone pain and arthritis, because 90% of adults with the complete, nonfamilial HOA syndrome have or will develop a malignancy.⁷⁴ A family history should screen for primary HOA or familial clubbing, which may preclude the need for further evaluation. A social history should screen for occupation exposure to asbestos, coal mine dust,⁷⁵ and pigeon breeding,³⁶ and risk factors for lung cancer, HIV, and tuberculosis. Physical examination should take note of lymphadenopathy, lung pathology, hepatomegaly, abdominal tenderness, and skin changes associated with thyroid disease or underlying malignancy (Fig 4).

Sometimes, despite extensive laboratory evaluation and imaging, no cause for digital clubbing is found and the patient must be reassured of the harmless nature of idiopathic clubbing, which may represent an incomplete form of primary HOA.⁷⁶ There are no published reports indicating what percentage of patients presenting with clubbing will eventually prove to have idiopathic clubbing.

PROGNOSIS AND TREATMENT

Clubbing has been studied widely as a prognostic factor. It has been suggested that its presence can be used to distinguish idiopathic pulmonary fibrosis from pulmonary fibrosis secondary to collagen vascular disease.⁷⁷ In cystic fibrosis,^{78,79} asbestosis,³⁵ hypersensitivity pneumonitis,³⁶ tuberculosis,⁸⁰ and idiopathic pulmonary fibrosis,⁸¹ clubbing has been associated with greater severity of disease or increased risk of mortality.

The prognosis of clubbing is completely dependent on the underlying process. If the primary process is identified and treated, clubbing usually reverses completely. Crohn's disease treated with removal of involved bowel,⁴² pleural tumors²⁹ treated with chemotherapy, hepatopulmonary syndrome treated with transplant,⁸² cystic fibrosis treated with transplant,⁸³ and whipworm treated with antimicrobials⁴⁸ have all been associated with reversal of digital clubbing. Indeed, the only recognized treatment for clubbing is treatment of the primary lesion; however, with the recent progress in our understanding of the pathogenesis of clubbing, antiplatelet and anticytokine therapy may one day prove useful in cases of idiopathic or familial clubbing.

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